

In vitro Diagnostics- Role in Efficacy Biomarker Assessment

Minimal Residual Disease (MRD) as a Surrogate
Endpoint in Acute Lymphoblastic Leukemia (ALL)
Workshop

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Leukemia Drug Development Using Novel or Abbreviated Endpoint

- Biomarker defines an endpoint that occurs prior to standard endpoint, e.g., PFS/OS
- Criterion: Use of biomarker is acceptable to therapeutic review office/division
 - One time (or case by case) agreement to allow use of biomarker
 - “Biomarker qualification” allows broader use of biomarker as “surrogate” under stated conditions of use
 - Biomarker is qualified, but particular test strategy, protocol, materials, are not
 - Cleared/approved test is NOT required, but strong evidence of analytical performance of intended system should be an expectation.

Biomarker \neq In Vitro Diagnostic Test

- Biological Marker: “A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”
 - Suitability for clinical management is not addressed
- In vitro diagnostic product: “...those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health...”
 - Safety and effectiveness for clinical management is evaluated in FDA review

CLIA \neq FFD&CA

- CLIA (via CMS) regulates clinical laboratories, not the tests that they perform.
- FFD&CA (via FDA, Device Amendments) regulates medical device manufacturers.
- The FFDCa affects both investigational and commercial testing (e.g., investigational LDTs still fall under FDA authority)

Analytical Validation

- Accuracy
 - Measurements represent the intended analyte
 - Measurements are not biased
- Reproducibility
 - Under “constant” conditions
 - Across systematically “varied” conditions
- Applicable standards (e.g., CLSI) can be useful

Clinical Validation

- Well-specified intended use
- Demonstrated safety and effectiveness for the intended use
 - Special attention to the intended use population
 - Special attention to “cut points” (cut-offs)

Effects Using Biomarker/Clinical Trial Test of Novel Endpoint

- Shorter clinical trials (smaller?)
- Correlation to traditional endpoint should be strong
 - Evidence of very convincing link of biomarker to traditional endpoint, across context of use
- Test versions across sites/trials can affect read-out
 - Need for standardization, validation, documentation
 - Possibilities:
 - Cleared/approved test
 - Agreed upon testing paradigm, including all validations and controls needed to establish comparable performance

Biomarker Qualification

- Programmatic qualification of *marker* handled by CDERs Office of Translational Science (OTS)
 - Requires package that establishes “clinical meaning” under specific context of use
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>
 - Qualification agreed to/declined by review team, including review divisions affected
 - Once established, anyone can use under same context
 - Has no effect on regulatory status of test
- One-time use simply agreed to under IND protocol; not transferable to other situations

In Vitro Diagnostic Product Uses

- Research use
- Investigational
use
- Diagnostic use

MRD Tests

- To date, NO tests for minimal residual disease cleared/approved for clinical management
 - Any use in CT would be investigational
- Use as endpoints in CT are pharmacodynamic in nature, but are similar to “prognostic” use suggested for clinical management
- Current technologies/markers vary
 - How do they compare?
 - Is one easier to use than another?
 - Can they be standardized?

Significant Risk (SR) Investigations

- SR: Investigational device presents potential for significant risk (of harm) to patient when used as proposed
- Investigational Device Exemption (IDE) review (or equivalent) required for SR investigations

IDE Review

- Subjects' safety
- Knowledge to be gained from investigation
- Alignment with plans for later development and FDA review

Non-Significant Risk (NSR) Investigations

- Investigation not exempt; results used in patient management but present little/no risk (of harm) to patient
- No submission to FDA required
- All relevant investigational requirements still apply

Device “ready” for use to guide accrual, treatment, or assess outcome in a clinical trial?

- Fully specified device, for purposes of the trial
- Analytical performance adequately assessed
- Pre-clinical or clinical information justifies subjects’ “exposure”
- Well-posed question or hypothesis can be answered/tested by the trial

Summary

- Substantial difference in approach for biomarker qualification, test clearance/approval, investigational use of test
- MRD currently not widely standardized in US, no approved/cleared tests
- Use as surrogate dependent on context of use (biomarker) as well as test performance (IVD)
- Investigational use in play
 - Use in trials
 - Use in standard clinical management?



Questions?

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

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